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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/889,321	07/13/2001	Yousuke Takahama	31671-173265	2334

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/889,321	TAKAHAMA, YOUSUKE	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *13-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

As discussed in the Pre-Brief Appeal Conference decision mailed to applicants on 4/12/06, the conference participants have decided to reopen prosecution of the instant application in view of new grounds of rejection. The finality of the action mailed on 10/21/05 is therefore withdrawn.

Claims 1-19 are pending in the instant application. This application contains claims 13-19 drawn to an invention non-elected without traverse in the response received on 11/03/03. Claims 13-19 are therefore withdrawn from prosecution. Claims 1-12 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

As noted in the Advisory Action mailed on 2/28/06, the rejection of claim 9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn over claim 9 in view of applicant's amendment to the claim.

Claim Rejections - 35 USC § 103

The rejection of claims 1-12 under 35 U.S.C. 103(a) as being unpatentable over Ilan et al. (1996) J. Clin. Invest., Vol. 98 (11), 2640-2647, in view of DeMatteo et al. (1997) J. Virol., Vol.

71 (7), 5330-5335, and further in view of Bakker et al. (1999) J. Immunol., Vol. 162, 3456-3462, is withdrawn. Applicant's arguments presented in the Pre-Appeal Brief Conference Request have been found persuasive in that it is agreed that specific motivation to substitute transfected fetal lymphocytes for the hepatocytes taught by Ilan et al. is not provided by DeMatteo et al. or Bakker et al.

The claims appear to be free of the prior art of record. While the prior art of record teaches methods of acquiring immune tolerance to foreign DNA and specification recombinant adenovirus and its protein expression products by introducing transduced cells, specifically hepatocytes, into the thymus (see Ilan et al.), and further teaches transducing fetal T lymphocytes *in vivo* or *in vitro* (see DeMatteo et al. and Bakker et al.), the prior art of record does not provide specific motivation to substitute transduced fetal T lymphocytes for transduced hepatocytes in the methods of acquiring immune tolerance taught by Ilan et al.

The following new grounds of rejection apply.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amendment to the claims filed on 8/19/04 amended claims 1, 2, and 8-10, deleting the words "fetal T lymphocytes" and replacing them with "immature T lymphocytes". The amendment did not point to where any support for an "immature T lymphocyte" can be found in the specification as filed. The specification does not contain any reference to an "immature T lymphocyte", the specification and claims as originally filed only teaches and recites fetal T lymphocytes. Thus, the specification lacks support for immature T lymphocytes. The recitation in the claims of "immature T lymphocytes" is therefore new matter. It is suggested that the applicant amend to the claims to recite " fetal T lymphocytes" to overcome this rejection.

Claims 1-12 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) methods of acquiring immunological tolerance to a foreign DNA and/or its expression product comprising: providing a fetal T lymphocyte transfected with the foreign DNA, irradiating a host mammal in order to transiently suppress T lymphocytes, and introducing the transfected fetal T lymphocyte into the thymus of the host mammal, wherein the introduced fetal T lymphocyte induces immunological tolerance to the foreign DNA and/or its expression product and 2) methods of sustaining the expression of a foreign gene by avoiding immune responses caused by the foreign gene and/or its expression

product comprising providing a fetal T lymphocyte transfected with the foreign gene, irradiating a host mammal in order to transiently suppress T lymphocytes, introducing the transfected fetal T lymphocyte into the thymus of the host mammal, wherein the introduced fetal T lymphocyte induces immunological tolerance to the foreign gene and its expression product, and administering the foreign gene, wherein the expression of the gene product is sustained, does not reasonably provide enablement for said methods wherein the transfected T lymphocyte is not a fetal T lymphocyte, wherein the host mammal has not been irradiated to suppress existing T lymphocytes, or wherein the gene product expressed has a therapeutic effect. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims as written broadly recite acquiring immunological tolerance to a foreign DNA and/or its expression product or methods of sustaining a gene therapeutic effect and avoiding immune response caused by a foreign gene, comprising introducing a transfected immature T lymphocyte into the thymus. The term "immature T lymphocyte" is broad and encompasses any non-mature T cell, including fetal cells and adult cells. However, as noted above in the rejection of the claims for new matter, the specification and claims as originally filed do not recite the term "immature T lymphocyte" or provide any description of what specific characteristics such as cell would possess. The specification and claims as filed only recites "fetal T lymphocytes", and only provides specific guidance for using fetal T lymphocytes to tolerize immune responses in a non-human mammal. This includes the working examples, which are limited to the use of fetal T lymphocytes derived from a day 14-18 mouse embryo. Thus, the specification as filed fails to provide any guidance as the characteristics of an "immature" T lymphocyte that would

allow it to be used successfully to induce immunological tolerance in the thymus, and further provides no guidance or evidence that any T lymphocyte other than a fetal T lymphocyte derived from a day 14-18 embryo can be transfected/transduced with foreign DNA and induce immunological tolerance to foreign DNA and its expression product when introduced into the thymus of a mammal. Thus, based on the breadth of the claims, and the lack of specific guidance provided by the specification, the specification fails to provide an enabling disclosure for how to identify and isolate an "immature" T lymphocyte, and to use that immature T cell to induce immunological tolerance to a foreign gene or gene product without undue experimentation.

It is further noted that the specification clearly teaches that prior to the introduction of the transduced fetal T lymphocytes into the thymus, the host is irradiated to transiently suppress existing host T lymphocytes, see pages 4 and 12. The claims as written read broadly on introducing the transfected immature T lymphocytes into the thymus of any animal, irradiated or non-irradiated. However, at the time of filing, it was well known that the presence of foreign proteins in the thymus is not capable of inducing tolerance of pre-existing mature T lymphocytes in the mammal (see for instance Oluwole et al. (1995) Cell. Immunol., Vol. 162, 33-41). Oluwole et al. demonstrates that while intrathymic injection of foreign protein results in the tolerization of new T lymphocytes, this tolerization does not affect mature T-cells already in the circulation (Oluwole et al., *supra,* page 39). Further, the state of the art of inducing central tolerance, i.e. where the foreign DNA or cells expressing the foreign DNA are directly administered to the thymus to induce tolerance, at the time of filing shows that the skilled artisan at least transiently suppressed mature T lymphocytes in the host prior to the intrathymic administration of the cells or vector (see Ilan et al. (1996) J. Clin. Invest., Vol. 98 (11), 2640-

2647 or DeMatteo et al. (1997) J. Virol., Vol. 71 (7), 5330-5335). Therefore, in view of the art recognized unpredictability in inducing immunological tolerance of pre-existing mature T lymphocytes by intrathymic injection of foreign protein, DNA, or transfected cells, the state of the art of central tolerance induction which included the transient suppression of mature T lymphocytes in the host, the limitation of the working examples to methods which include transient suppression of mature T lymphocytes in the host with irradiation, the lack of guidance in the specification for inducing immunological tolerance in mature T lymphocytes, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed in the absence of transient T cell suppression in the host.

The specification further fails to provide an enabling disclosure for sustaining gene therapeutic effects in gene therapy using the claimed methods. The specification, while broadly drawn to sustaining the expression of a foreign gene by inducing tolerance through intrathymic administration of fetal T lymphocytes transfected with the foreign gene, reads on the expression of sustaining therapeutic levels of the gene in the mammal and on gene therapy of disease. The specification provides guidance as to several genes to be introduced using the applicant's methods, including genes coding for substances causing allergic or autoimmune diseases, genes coding for peptide anti-cancer agents or for peptide pharmaceutical medicaments for diabetes or the like. However, the specification does not provide any specific guidance as to any particular vector or gene which is capable of having a therapeutic effect on any disease or disorder and further fails to provide and specific guidance for treating diseases such as cancer, diabetes, rheumatoid arthritis, or multiple sclerosis. It is further noted that the working example utilizes DNA encoding a marker protein as the foreign gene and does not correlate the level, location, or

duration of expression of the marker in either the thymus or in any other organ following subsequent non-thymic administrations of the foreign DNA with the level, location, and duration of expression of a therapeutic gene product required to treat any disease or disorder.

At the time of filing, gene therapy of disease, whether by direct administration of vectors or by the administration of transfected cells, was considered highly unpredictable. Verma et al. teaches that," ... the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable challenges" in gene therapy, and specifically identifies the "Achilles heel" of gene therapy as gene delivery (Verma et al. (1997) Nature, Vol. 389, page 239, column 1, paragraph 1, and column 3, paragraph 2). In particular, Verma points out that, " [a] critical limitation of retroviral vectors is their inability to infect non-dividing cells, such as those that make up muscle, brain, lung, and liver tissue " (Verma et al. (1997) Nature, Vol. 389, page 240, column 1, paragraph 3). Verma also teaches that the choice of an appropriate enhancer-promoter combination is critical to the level and consistency of gene expression from a particular vector and that , " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al. (1997) Nature, Vol. 389, page 240, column 2, paragraph 2, and column 3, line 1). Orkin et al. concurs, stating that, "[m]ajor difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", and that "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol.." (Orkin et al. (1995) Report to the NIH, page 1, paragraphs 3-4). Freidmann further supports the statements made by Orkin et al. by stating in a recent of the progress in gene therapy of disease that, "[s]o far, however, no approach has definitively

improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (Freidmann (1997) Scientific American, Vol. , page 96, column 2, paragraph 1). Thus, in view of the art recognized high degree of unpredictability in achieving therapeutic levels of gene expression *in vivo* capable of treating disease, the lack of guidance provided by the specification for specific therapeutic genes, and the required level and duration of expression of those genes in particular target cells necessary to treat any condition or disease in a subject, the lack of correlation between applicant's working examples and any therapeutic effect on any disease or condition, and the breadth of the claims, it would have required undue experimentation to practice the instant invention as claimed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the

USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER